

## Discordance Between Ambulatory Monitoring and Programmed Stimulation in Assessing Efficacy of Class IA Antiarrhythmic Agents in Patients With Ventricular Tachycardia

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Concordance between programmed stimulation and 24 hour ambulatory electrocardiographic (Holter) monitoring was studied in 54 patients with sustained ventricular tachycardia during 84 therapeutic trials with class IA antiarrhythmic agents. During baseline studies before treatment, all patients had frequent ( $\geq 30/h$ ) ventricular premature complexes on Holter recordings and sustained ventricular tachycardia inducible by one to three extrastimuli. During treatment, programmed stimulation and Holter monitoring were repeated. Efficacy of treatment determined by programmed stimulation (ventricular tachycardia no longer inducible or nonsustained) was compared with three Holter criteria of efficacy: I = 83% or more reduction of ventricular premature complexes and abolition of ventricular tachycardia; II = 50% or more reduction of ventricular premature complexes and 90% or more reduction of couplets and abolition of ventricular tachycardia; III = abolition of ventricular tachycardia in patients with ventricular tachycardia during a baseline Holter recording.

Treatments were judged effective by programmed stimulation criteria in only 25% of cases but in 51, 63

and 75% of cases by Holter criterion I, II and III, respectively. Results of programmed stimulation and Holter monitor were discordant (effective by one criterion but ineffective by the other) in 50% of cases using Holter criterion I, in 54% using Holter criterion II and in 61% using Holter criterion III. In the majority of discordant results, treatments appeared efficacious by Holter criteria but ineffective by programmed stimulation criteria, suggesting insensitivity of efficacy by Holter criteria or nonspecificity of induced ventricular tachycardia during treatment, or both.

**Conclusions:** 1) programmed stimulation and Holter monitor recording are discordant in assessing efficacy of class IA antiarrhythmic agents; 2) efficacy by Holter criteria is often easier to achieve than efficacy by programmed stimulation ( $p < 0.001$ ); and 3) the discordance between the two methods, both with very good reported predictive values, calls for long-term follow-up studies to determine sensitivity and specificity of each method.

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There are different approaches to the management of patients with sustained symptomatic ventricular tachycardia or out of hospital cardiac arrest (1-10). Two commonly used approaches are 1) programmed stimulation (5-10), and 2) reduction of frequent and complex ventricular premature complexes using ambulatory (Holter) monitoring (1-4). Each approach has been used individually by many investigators (1-10) with very good reported predictive value. However,

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data regarding any correlation between programmed stimulation and ambulatory monitoring are limited (11), and no study has been done to determine the degree of concordance between programmed stimulation and Holter monitoring in assessing the efficacy of antiarrhythmic agents. To evaluate the correlation between these two approaches we have applied both programmed stimulation and ambulatory monitoring concurrently in 54 patients with recurrent sustained ventricular tachycardia with hemodynamic compromise or ventricular fibrillation during 84 treatments with class IA antiarrhythmic agents.

### Methods

**Patient selection.** Fifty-four patients were studied. They all had recurrent sustained ventricular tachycardia with

hemodynamic compromise or ventricular fibrillation. None of the arrhythmias was associated with acute myocardial infarction or remediable causes (such as hypokalemia, digoxin toxicity or drug-induced arrhythmia). Criteria for admission to the study also included frequent ( $\geq 30/h$ ) ventricular premature complexes on Holter monitoring (1,12) and inducible sustained (13,14) ventricular arrhythmia by programmed stimulation requiring intervention for termination during a baseline study in the absence of antiarrhythmic agents.

**Ambulatory electrocardiographic monitoring.** Continuous 24 hour ambulatory electrocardiograms were recorded on an Avionics 445 two-channel recorder. Analysis of the tape was done on a computerized Cardio Data System scanner. The total number of ventricular premature complexes, couplets and nonsustained ventricular tachycardia ( $\geq 3$  ventricular premature complexes at a rate faster than 100 beats/min) were generated by the scanner. Accuracy of the system was tested by the blind insertion of quality control tapes into the analyst's normal work load. Standard data used for accuracy determination were generated through trendscription of the entire 24 hour period; the recorded data were then hand-counted for quantification of all ventricular ectopic activity.

*Accuracy was calculated using the following formula:*

$$100 - \frac{(HS - RT)}{RT} \times 100 = \text{accuracy (\%)},$$

where HS = high speed and RT = real time. Accuracy of total ventricular premature complex count was  $96.3 \pm 3.7\%$ , couplets  $93.7 \pm 6.7\%$  and ventricular tachycardia  $96.2 \pm 5.8\%$ . The results were verified by one of the investigators. Mean ventricular premature complex count or couplets was calculated by dividing the total number of ventricular premature beats or couplets by the number of hours recorded.

**Programmed stimulation.** Programmed stimulation was performed initially at the right ventricular apex in all patients. When ventricular tachycardia was not inducible at the right ventricular apex, the right ventricular outflow tract was stimulated. Single ( $S_2$ ), double ( $S_2S_3$ ) or triple ( $S_2S_3S_4$ ) premature stimuli were introduced during sinus rhythm ( $S_1S_1$ ) and during ventricular pacing ( $S_1S_1$ ) at cycle lengths of 600 to 400 ms. A single premature stimulus ( $S_2$ ) was introduced in late diastole and the coupling interval was gradually shortened by 10 ms until ventricular tachycardia was induced or until the effective refractory period of the ventricle was reached. When double extrastimuli ( $S_2S_3$ ) were necessary for induction of ventricular tachycardia,  $S_2$  was introduced at an interval 10 ms longer than the effective refractory period and  $S_3$  was introduced at gradually shorter coupling intervals until ventricular tachycardia was induced or until the effective refractory period was reached. A third extrastimulus ( $S_4$ ) was introduced, if needed, in a manner analogous to that for  $S_3$ .

**Study design.** Informed consent was obtained from all

patients before the study for serial drug testing by programmed stimulation and ambulatory electrocardiographic monitoring. All patients had a baseline 24 hour ambulatory electrocardiogram and programmed stimulation study at least five half-lives after discontinuation of all antiarrhythmic medications. If needed for other reasons, digoxin or propranolol, or both, was continued throughout the study. After the baseline studies, administration of a class IA antiarrhythmic agent (procainamide, quinidine or disopyramide) was started. The dose of the agent was adjusted to the maximum as tolerated by the patient. Programmed stimulation and 24 hour ambulatory monitoring were repeated after the patient had received an antiarrhythmic agent at a constant dose for at least five doses to ensure steady state blood levels. Some patients were studied sequentially taking more than one agent, each used separately, by concurrent ambulatory monitoring and programmed stimulation.

**Data analysis.** Results of concurrent ambulatory monitoring and programmed stimulation during each treatment in each patient were compared for concordance of efficacy. Three criteria were used for efficacy by Holter monitoring:

*Criterion I* = 83% or greater reduction of ventricular premature complexes (15) and abolition of ventricular tachycardia (1-4).

*Criterion II* = 50% or greater reduction of ventricular premature complexes and 90% or greater reduction of couplets and abolition of ventricular tachycardia (1,2).

*Criterion III* = abolition of ventricular tachycardia in patients who had ventricular tachycardia during a baseline Holter recording (3,4).

**Programmed stimulation criteria.** A treatment was considered effective when previously induced ventricular tachycardia was no longer inducible (5-10) or nonsustained ( $\leq 15$  beats in duration) (16).

**Statistical analysis.** Concordance or discordance between ambulatory monitoring and programmed stimulation in assessing efficacy or inefficacy of drugs was tested by McNemar's test.

## Results

**Patient characteristics.** Of the 54 patients studied, 46 were men and 8 were women with an average age ( $\pm$  SD) of  $58 \pm 12$  years. Fifty-one patients had symptomatic recurrent sustained ventricular tachycardia; in three patients, the first documented arrhythmia was ventricular fibrillation. Forty-seven patients had coronary artery disease with previous myocardial infarction, six had cardiomyopathy and one had mitral valve prolapse syndrome.

**Drug treatment.** For this study, 30 of 54 patients received quinidine, 24 procainamide and 30 disopyramide. Some patients were studied taking more than one agent, each used separately. The mean daily dosage of quinidine was  $1,600 \pm 210$  mg, procainamide  $4,000 \pm 885$  mg and disopyramide  $933 \pm 308$  mg.

**Table 1.** Results of Ambulatory Electrocardiographic Monitoring in 54 Patients

	Quinidine (n = 30)		Procainamide (n = 24)		Disopyramide (n = 30)	
	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx
VPCs/h	279 ± 40	44 ± 59	355 ± 326	104 ± 166	323 ± 362	58 ± 95
Pts. with ≥83% reduction	—	18 (60%)	—	11 (46%)	—	18 (60%)
Pts. with ≥50% reduction	—	24 (80%)	—	21 (88%)	—	27 (90%)
Couplets/h	10.5 ± 28.2	0.8 ± 1.7	13.7 ± 17.4	2.4 ± 8.4	10.5 ± 15.9	3.7 ± 10.8
Pts. with/without couplets	27/3	18/12	22/2	12/12	28/2	15/15
Pts. with ≥90% reduction	—	14 of 27	—	16 of 22	—	22 of 28
VT/24 h	41.5 ± 149.2	0.7 ± 2.3	49.9 ± 157.5	3.9 ± 18.1	32.5 ± 74.4	5.1 ± 20.3
Pts. with/without VT	19/11	6/24	16/8	4/20	22/8	4/26
Pts. with abolition of VT	—	13 of 19	—	12 of 16	—	18 of 22

n = number of patients; Post = after; Pre = before; Pts. = number of patients; Rx = treatment; VPCs = ventricular premature complexes; VT = ventricular tachycardia (≥ three ventricular premature complexes in a row at rate greater than 100/min).

**Ambulatory electrocardiography (Tables 1 and 2).** Quinidine was effective in 15 (50%) of 30 patients by Holter criterion I, 14 (47%) of 30 by Holter criterion II and 13 (68%) of 19 by Holter criterion III. Procainamide was effective in 10 (42%) of 24 patients by criterion I, 15 (63%) of 24 by criterion II and 12 (75%) of 16 by criterion III. Disopyramide was effective in 18 (60%) of 30 patients by criterion I, 24 (80%) of 30 by criterion II and 18 (82%) of 22 by criterion III.

**Programmed stimulation (Tables 2 and 3).** All 54 patients, including 3 whose first documented rhythm was ventricular fibrillation, had sustained monomorphic ventricular tachycardia induced by one, two or three extrastimuli before treatment requiring rapid ventricular pacing or direct current cardioversion for termination. Ventricular tachycardia was induced by double extrastimuli during sinus rhythm in 1 patient, by triple extrastimuli during sinus rhythm in 14, by single extrastimuli during ventricular pacing in 3, by double extrastimuli during ventricular pacing in 8 and by triple extrastimuli during ventricular pacing in 28 patients. Thus, ventricular tachycardia was induced by one or two extrastimuli in only 12 patients (22%), by three extrastimuli during sinus rhythm in 14 patients (26%) and by three extrastimuli during ventricular pacing in 28 patients (52%).

Treatment was effective by programmed stimulation criteria in 8 (27%) of 30 patients taking quinidine, 5 (21%) of 24 taking procainamide and 8 (27%) of 30 taking disopyramide. In patients who had inducible ventricular tachycardia after treatment, the cycle length of induced ventric-

ular tachycardia was significantly ( $p < 0.05$ ) longer after treatment compared with baseline study.

**Concordance between programmed stimulation and Holter monitoring (Table 4).** Efficacy of treatment determined by programmed stimulation criteria was compared with efficacy determined by the three Holter criteria. Assessments of efficacy by programmed stimulation and by Holter monitoring criterion I were concordant in 42 treatments (50%) and discordant in 42 (50%). Programmed stimulation and Holter criterion II assessments were concordant in 46% and discordant in 54%. Programmed stimulation and Holter criterion III assessments were concordant in 39% and discordant in 61%. When quinidine, procainamide and disopyramide were considered individually, similar rates of discordance were noted. By Holter criterion I, discordance was noted in 57% of the patients taking quinidine, 37% of those taking procainamide and 53% of those taking disopyramide. By Holter criterion II, discordance was noted in 53% of the patients taking quinidine, 50% of those taking procainamide and 60% of those taking disopyramide. By Holter criterion III, discordance was noted in 58% of the patients taking quinidine, 50% of those taking procainamide and 73% of those taking disopyramide.

In the majority of the discordant results, a treatment was considered effective by Holter criteria but ineffective by programmed stimulation criteria. Using Holter criterion I, in 32 (76%) of 42 discordant assessments treatment was considered effective by Holter monitoring but ineffective by programmed stimulation, whereas in 10 (24%) treatment

**Table 2.** Efficacy of Treatment Determined by Programmed Stimulation and Holter Monitoring

	Quinidine	Procainamide	Disopyramide	All Treatments
Programmed stimulation	8 (26%)	5 (21%)	8 (26%)	21 (25%)
Holter criterion I*	15 (50%)	10 (42%)	18 (60%)	43 (51%)
Holter criterion II*	14 (47%)	15 (63%)	24 (80%)	53 (63%)
Holter criterion III*	13 (68%)	12 (75%)	18 (82%)	43 (75%)

\*See text for description of the three Holter efficacy criteria.

**Table 3.** Results of Programmed Stimulation in 54 Patients

	Quinidine (n = 30)		Procainamide (n = 24)		Disopyramide (n = 30)	
	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx
Pts. with VT induced by PES*	30	22	24	19	30	22
SR + 1 PES	0	0	0	0	0	0
SR + 2 PES	1	1	1	0	0	5
SR + 3 PES	6	4	1	4	9	3
VP + 1 PES	3	0	1	1	3	2
VP + 2 PES	7	8	1	4	7	4
VP + 3 PES	13	9	20	10	11	8
VT cycle length (ms)	280 ± 58	335 ± 67	256 ± 55	312 ± 57	273 ± 55	388 ± 88

\*All patients had inducible sustained ventricular tachycardia before treatment. After treatment, the number of patients with sustained ventricular tachycardia or tachycardia longer than 15 beats are shown. PES = programmed extrastimuli; SR = sinus rhythm; VP = ventricular pacing; other abbreviations as in Table 1.

was ineffective by Holter monitoring but effective by programmed stimulation. Using Holter criterion II, treatment was considered effective by Holter monitoring in 39 (85%) of 46 discordant assessments but in only 7 (15%) by programmed stimulation. By Holter criterion III, treatment was effective by Holter monitoring in 32 (91%) of 35 discordant assessments and in only 3 (9%) by programmed stimulation criteria. Thus, Holter monitoring and programmed stimulation were discordant in more than 50% of efficacy assessments. When the two methods were discordant, it was more likely that a treatment was judged effective by Holter criteria than by programmed stimulation criteria ( $p < 0.001$  by McNemar's test).

## Discussion

Our study suggests that 1) assessment of efficacy of class IA antiarrhythmic agents determined by programmed stim-

ulation and Holter monitoring is often discordant; 2) treatment is considered effective more frequently by Holter criteria than by programmed stimulation criteria; and 3) treatment considered to be ineffective by programmed stimulation is often considered effective by Holter criteria.

Patients with fewer than 30 ventricular premature complexes/h were excluded from this study because it is the consensus (1,12) that such patients should be managed by programmed stimulation rather than by Holter monitoring.

**Programmed stimulation protocol: role of triple extrastimuli.** The specificity of polymorphic nonsustained ventricular tachycardia induced by triple extrastimuli has been questioned in patients whose documented ventricular tachycardia is monomorphic (13,14). However, in a significant number of patients with recurrent ventricular tachycardia, triple extrastimuli are necessary to induce clinical arrhythmia and this is considered to be specific (10,13, 14,16,17). In our study, most patients required triple ex-

**Table 4.** Correlation Between Efficacy of Treatments Determined by Programmed Stimulation and Holter Monitoring

	Q (n = 30)	PA (n = 24)	D (n = 30)	All Treatments (n = 84)
PES vs. Holter I*: concordance (Rx effective by both)	3	3	5	11 (13%)
PES vs. Holter I: concordance (Rx ineffective by both)	10	12	9	31 (37%)
PES vs. Holter I: discordance (effective only by Holter)	12	7	13	32 (38%)
PES vs. Holter I: discordance (effective only by PES)	5	2	3	10 (12%)
Discordance by McNemar's test	$p < 0.2^{\dagger}$	$p < 0.2^{\dagger}$	$p < 0.025$	$p < 0.001$
PES vs. Holter II*: concordance (Rx effective by both)	3	4	7	14 (17%)
PES vs. Holter II: concordance (Rx ineffective by both)	11	8	5	24 (29%)
PES vs. Holter II: discordance (effective only by Holter)	11	11	17	39 (46%)
PES vs. Holter II: discordance (effective only by PES)	5	1	1	7 (8%)
Discordance by McNemar's test	$p < 0.2^{\dagger}$	$p < 0.01$	$p < 0.001$	$p < 0.001$
	Q (n = 19)	PA (n = 16)	D (n = 22)	All (n = 57)
PES vs. Holter III*: concordance (Rx effective by both)	4	3	3	10 (18%)
PES vs. Holter III: concordance (Rx ineffective by both)	4	5	3	12 (21%)
PES vs. Holter III: discordance (effective only by Holter)	9	8	15	32 (56%)
PES vs. Holter III: discordance (effective only by PES)	2	0	1	3 (5%)
Discordance by McNemar's test	$p < 0.1^{\dagger}$	$p < 0.01$	$p < 0.005$	$p < 0.001$

\*See text for efficacy criteria by programmed stimulation and Holter monitoring;  $^{\dagger}p = \text{NS}$ . D = disopyramide; PA = procainamide; Q = quinidine; other abbreviations as in Tables 1 and 3.

trastimuli for induction of sustained ventricular tachycardia during baseline study in the absence of antiarrhythmic drugs. Therefore, efficacy by programmed stimulation was defined as noninducibility of ventricular tachycardia or occurrence of nonsustained ventricular tachycardia ( $\leq 15$  beats) after three extrastimuli. The reason most of our patients required three extrastimuli for induction of ventricular tachycardia during baseline study is unclear. It may be related to the stimulation protocol or the patient group at our institution.

**Holter monitoring.** Because of spontaneous variability in ventricular arrhythmia (15), a longer period of monitoring (such as 72 hours) could possibly have affected the results of the study; however, the rigor of our efficacy criteria and the fact that all patients had Holter monitoring for at least 24 hours, often for 48 hours, probably minimize the effect of spontaneous variability. Efficacy criteria used in this study (see Methods section) are used widely by many investigators (1-10,15,16).

**Discordance between programmed stimulation and Holter monitoring.** This study suggests discordance between these two methods in evaluating efficacy of class IA antiarrhythmic agents. Concordance (effective or ineffective by both methods) was noted in less than 50% of the treatments. There are several inferences to be drawn from the discordant results seen in this study. Because the predictive value of efficacy by Holter monitoring has been reported to be very good (1-4), as has the predictive value of programmed stimulation (5-10), the discordance between the two methods is difficult to explain. When the two methods were discordant, a treatment was more likely to be effective by Holter criteria than by programmed stimulation criteria. This may suggest poor sensitivity (false efficacy) of suppression of ventricular premature complexes or poor specificity (false inefficacy) of ventricular tachycardia induced by programmed stimulation, or both, in a patient taking a class IA antiarrhythmic agent.

Poor specificity of ventricular tachycardia induced by programmed stimulation in patients taking amiodarone has been reported (18,19). However, there have been no previous reports of poor specificity of ventricular tachycardia induced by programmed stimulation in patients taking a class IA agent. Platia and Reid (11) reported a poor predictive value of negative results of ambulatory monitoring compared with negative results on programmed stimulation. However, as they noted, their study had major limitations. Ambulatory electrocardiographic monitoring and programmed stimulation were performed only on the discharge regimen, but not before treatment. Because a significant number of patients with recurrent ventricular tachycardia or fibrillation have negative results on Holter monitoring (without frequent or high grade ventricular premature complexes) even before treatment (1,12), many patients who had negative findings on ambulatory monitoring on the discharge regimen might also have had negative findings on ambu-

latory monitoring before treatment and should have been excluded in determining the predictive value of a negative Holter recording. Similar arguments may apply to programmed stimulation. To assess the value of a negative test result (using programmed stimulation or Holter monitoring) in determining efficacy of antiarrhythmic agents, the test must be performed before treatment with antiarrhythmic agents to exclude the patients with a negative test result before treatment.

In brief, there are no studies that adequately compare the predictive accuracies of Holter monitoring and programmed stimulation in the assessment of efficacy of class IA antiarrhythmic agents. Our study was not designed to answer this important question. Although one might be more confident about efficacy or inefficacy of a treatment when results of Holter monitoring and programmed stimulation are concordant, discordance between the two tests poses a dilemma in patient management. Independent studies of these two methods may be influenced by such factors as selection criteria, variations in stimulation protocol, investigator bias and differences in follow-up management. Thus, the question of which method offers a superior predictive accuracy can only be answered by a concurrent, randomized trial with long-term clinical follow-up.

Our study involved selected patients, mostly with coronary artery disease, with frequent ventricular premature complexes and inducible ventricular tachycardia. The results may be different in different patient groups taking a different class of antiarrhythmic agents. Further study will be necessary to answer this question.

**Conclusions.** In patients with inducible sustained ventricular tachycardia and frequent ventricular premature complexes before treatment: 1) programmed stimulation and Holter monitoring are often discordant in assessing efficacy or inefficacy of procainamide, quinidine and disopyramide; 2) efficacy by Holter criteria is often easier to achieve than efficacy by programmed stimulation; and 3) the discordance between the two methods, both with very good reported predictive values, calls for long-term randomized clinical follow-up studies to determine sensitivity and specificity of each method.

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